

in a medium containing the first mitogen and the second mitogen, with the proviso that the second mitogen is other than the first mitogen.

REMARKS

Reconsideration and allowance in view of the foregoing amendments and the following remarks are respectfully requested.

Applicants and their legal representative wish to acknowledge the helpful and construction interview held with the Examiner on November 14, 2001. This Amendment results, in part, from that interview.

Claims 1-22 are presently pending in this application. Claims 1-5 and 12-16 stand rejected and claims 6-11 and 17-22 have been withdrawn from consideration. By this Amendment, claims 2-3, 6-11, 13-14 and 17-22 have been canceled and claims 1 and 12 have been amended. A clean copy of the claims after amendment is included in the attached Appendix.

Claim 1 has been amended by incorporating the specific recitations of claims 2 and 3. Accordingly, claims 2 and 3 have been canceled. Likewise, claim 12 has been amended by

incorporating the specific recitations of claims 13 and 14.

Accordingly, claims 13 and 14 have been canceled.

Thus, no new matter has been added by any of these amendments.

Specification

On page 3, in numbered paragraph 2, of the Official Action, the Examiner requires new application papers with lines double spaced on good quality paper. In response, Applicants are enclosing herewith the new application papers meeting the necessary requirements.

Information Disclosure Statement

On page 3, in numbered paragraph 3, of the Official Action, the Examiner indicates that the Information Disclosure Statement filed January 30, 2000 fails to comply with the requirements of 37 CFR 1.98(a)(2). On November 14, 2001, Applicants hand delivered to the Examiner the Information Disclosure Statement and a legible copy of each U.S. and foreign patent, and each publication, as previously filed on December 29, 1999, along with four additional scientific publications.

Claim Rejections - 35 USC § 112

On pages 3-4, in numbered paragraph 4, of the Official Action, the Examiner rejects claims 1-5 and 12-16 under 35 USC 112, first paragraph, as based on a disclosure which is not enabling. In this rejection, it is the position of the Examiner that the c-myc construct, c-myc gene, or "other DNA elements", required for carrying out step (c) are critical or essential to the practice of the invention but not included in the claims, are not enabled by the disclosure.

This rejection is respectfully traversed. First, the expression "other DNA elements" has been deleted from claims 1 and 12, thereby rendering this part of the rejection moot.

Second, case law provides that enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention. It is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive. Enablement is determined as of the filing date of the patent application. Furthermore, a patent need not teach, and preferably omits, what is well

known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986).

It is respectfully submitted that as of September 20, 1999, the filing date of the present application, persons of ordinary skill in the art knew what structurally constituted the necessary c-myc constructs and the c-myc DNA. The attached Declaration of Dr. Karl K. Johe presents evidence in support thereof.

First, the present application (page 4, line 21; and page 7, line 8) discloses the reference by Eilers et al. (Nature 340: 60-68, 1989) for the human c-myc DNA and the human estrogen receptor DNA, which is sufficient for those of ordinary skill in the art to make and use the invention disclosed in the present application. Copies of the references cited by Eilers et al., that is, Stone et al. for the structure of the c-myc DNA and Kumar et al. for the structure of the human estrogen receptor DNA, were provided with the Information Disclosure Statement hand delivered to the Examiner on November 14, 2001.

Second, as of September 20, 1999, the publicly available GenBank DNA database contained the complete cDNA sequences of the human c-myc DNA and the human estrogen

receptor DNA. Copies of two of the references cited in the GenBank DNA database, that is Green et al. for the sequence of the human estrogen receptor DNA and Watt et al. for the sequence of the c-myc DNA, were provided with the Information Disclosure Statement hand delivered to the Examiner on November 14, 2001.

Third, at least 10 scientific articles and patents submitted with the Information Disclosure Statement, filed December 29, 1999, in the present application relate to the c-myc constructs and the c-myc DNA. For example, U.S. Patent 5,580,777 (Bernard et al.), cited by the Examiner in the claim rejections under 35 USC 103, referred to the c-myc constructs and the c-myc DNA by reference to numerous scientific articles (see, for example, column 1, lines 62-64; column 4, lines 54-61).

Therefore, it is clear that as of September 20, 1999, persons of ordinary skill in the art knew what structurally constituted the necessary c-myc constructs and the c-myc DNA.

In view of the above, it is respectfully requested that this rejection be withdrawn and that claims 1, 4-5, 12 and 15-16 be allowed.

On pages 4-5, in numbered paragraph 5, of the Official Action, the Examiner rejects claims 1-5 and 12-16 under 35 USC 112, second paragraph. In this rejection, it is the position of the Examiner that the claims are indefinite.

In response, Applicants have amended claims 1 and 12 to overcome this rejection. In view of these amendments, it is respectfully requested that this rejection be withdrawn and that claims 1, 4-5, 12 and 15-16 be allowed.

On page 5, in numbered paragraph 6, of the Official Action, the Examiner rejects claims 1-5 and 12-16 under 35 USC 112, second paragraph. In this rejection, it is the position of the Examiner that the claims are incomplete for omitting essential steps.

In response, Applicants have amended claims 1 and 12 to overcome this rejection. In addition, case law provides that claims are read in the light of the disclosure of the specification on which they are based, not in a vacuum. *In re Dean*, 130 U.S.P.Q. 107 (C.C.P.A. 1961). Furthermore, one does not look to claims to find out how to practice the inventions they define, but, rather, to the specification. *In re Rainer et al.*, 134 U.S.P.Q. 343 (C.C.P.A. 1962).

In view of the above, it is respectfully requested that this rejection be withdrawn and that claims 1, 4-5, 12 and 15-16 be allowed.

Claim Rejections - 35 USC § 103

On pages 5-7, in numbered paragraph 7, of the Official Action, the Examiner rejects claims 1, 4-5, 12 and 15-16 under 35 USC 103(a) as being unpatentable over Bernard et al. (U.S. Patent 5,580,777) in view of Weiss et al. (U.S. Patent 5,851,832). In this rejection, it is the position of the Examiner that claims 1, 4-5, 12 and 15-16 are obvious over the combination of the teachings of the cited references.

This rejection is respectfully traversed. In an effort to advance the prosecution of this application and without acceding to the position of the Examiner, Applicants have amended claims 1 and 12 by incorporating the specific recitations of claims 2-3 and 13-14, respectively. In view of these amendments, it is respectfully submitted that the cited references fail to disclose or suggest the unexpected results obtained with the methods of amended claims 1 and 12.

More specifically, one major limitation for the commercial application of neural stem cells is that the mitotic capacity of the cells is finite (up to about 30 doublings) *in vitro*. This limitation is most likely caused by an intrinsic mechanism by the cells to regulate their own cell number, such as secreting an autocrine factor that antagonizes the mitogen action. The present invention is a method to overcome this mitotic limitation of neural stem cells in culture without affecting their differentiation potential, especially to neurons. The result is that one can expand neural stem cells in culture to a significantly greater extent and with far greater ease.

The key innovative aspect of the method is the realization that maintaining the intracellular level of c-myc, an endogenous cell-cycle regulating protein, is crucial to maintain neural stem cells in the mitotic state and in the multipotential state. The method then intends to provide an exogenous source of c-myc protein whose activity level within the cell can be controlled by an extracellular element. Such controllable exogenous c-myc protein is achieved in two ways. One way is to transfer to the cells a cDNA encoding an active c-myc, which is under

the control of a promoter inducible by an extracellular element such as tetracycline in the culture medium. The other way is to transfer to the cells a cDNA encoding an active c-myc, which is fused to a second cDNA encoding an active ligand binding domain of a steroid receptor. Both approaches have been successfully used to control expression of other genes. It is thought that the role of the ligand binding domain of a steroid receptor is to localize, upon binding to a ligand supplied in the culture medium, the c-myc fusion protein to the nucleus, thus rendering the c-myc portion of the protein to be functionally active.

It follows that the combination of the teachings of the cited references fails to disclose or suggest the unexpected results obtained with the methods of amended claims 1 and 12. It is, therefore, respectfully requested that this rejection be withdrawn and that claims 1, 4-5, 12 and 15-16, as amended, be allowed.


All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited.

YANG ET AL. -- U.S. PATENT APPLICATION 09/398,897

Should any matters remain in this application which might be resolved by interview, the Examiner is requested to telephone the undersigned at (570) 386-5744.

Respectfully submitted,

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APPENDIX